New practical synthesis of non-cross-linked polystyrene supported 2-phenylimino-2-oxazolidine

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A new practical method for the synthesis of a non-cross-linked polystyrene supported 2-phenylimino-2-oxazolidine chiral auxiliary is reported. This method started from the same material as in a previous synthesis, N-Boc-*L*-tyrosine ethyl ester, but the overall yield was 42.5%, which was higher than the copolymerisation method.

Keywords: practical, synthesis, non-cross-linked polystyrene, support, 2-phenylimino-2-oxazolidine

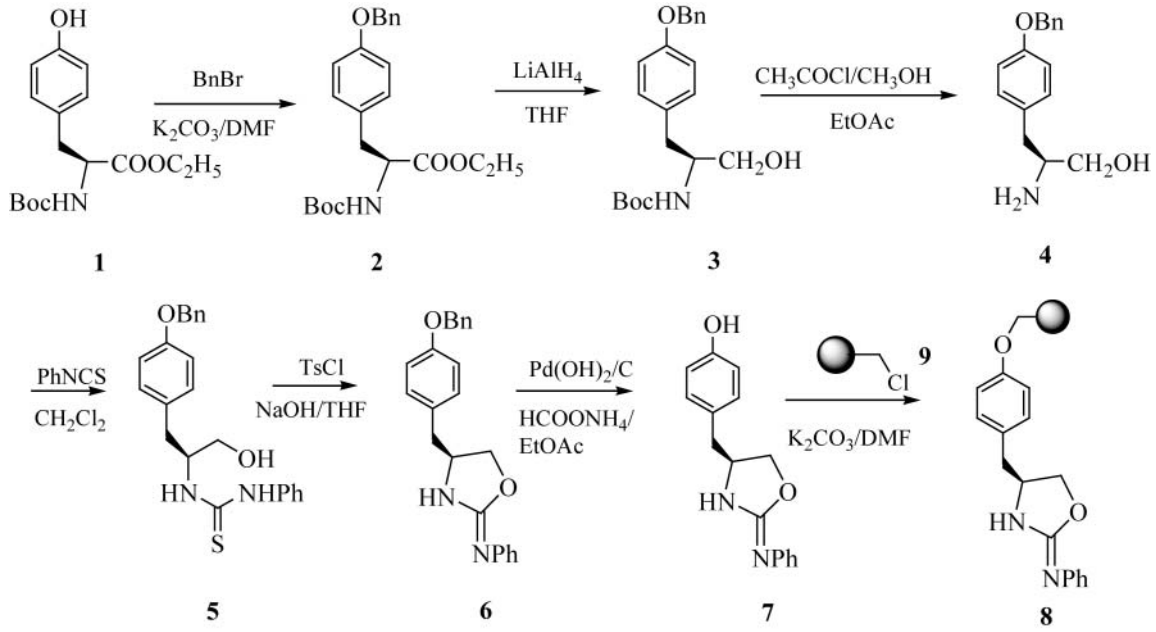
Asymmetric reactions using a chiral auxiliary have been studied extensively and are now important and useful methods for asymmetric carbon–carbon bond formation. Recently, a new class of chiral auxiliary 2-phenylimino-2-oxazolidine has been developed.[1] The auxiliary provides a superior performance to many other chiral auxiliaries currently in common use, and has been proved to be particularly efficient in terms of stereoselectivity and yield in asymmetric alkylations.[2,3] However, in most cases, the chiral auxiliaries cannot be effectively recovered after the reaction.

Insoluble polymer supports, such as the Merrifield resin and Wang resin provide a simple procedure involving "filtration" for rapidly achieving the isolation of desired compounds and recovering expensive reagents or catalysts attached to a solid-support for recycling.[4,5] However, it is difficult with some chiral auxiliaries to achieve a high degree of stereoselectivity in solid-supported reactions.[6] The soluble polymer supports, which combine the benefits of an insoluble polymer support with the advantages of classic liquid synthesis, have been extensively studied by chemists.[7–10] Our group has undertaken a research program to develop several chiral auxiliaries using non-cross-linked polystyrene (NCPS) as the support.[11–14] We have prepared NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary by the copolymerisation method[15]. We now report a new practical method to synthesise NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary (Scheme 1).

Results and discussion

As shown in Scheme 1, NCPS supported 2-phenylimino-2-oxazolidine was synthesised using N-Boc-*L*-tyrosine ethyl ester as the starting material. O-Benzyl-*L*-tyrosinol **4** can be conveniently obtained from N-Boc-*L*-tyrosine ethyl ester **1** according to the reported procedure in 58.5% overall yield.[16] Treatment of **4** with phenyl isothiocyanate yielded the thiourea **5** in 97% yield. 2-Phenylimino-2-oxazolidine **6** was easily obtained in 93% yield by the cyclization of the thiourea **5** using TsCl and NaOH. Removal of the benzyl group of **6** was carried out by 20% $Pd(OH)_2/C$ and $HCOONH_4$ to provide the compound **7** in the yield of 95%. Then **7** was attached to the functionalised NCPS **9** to afford NCPS supported 2-phenylimino-2-oxazolidine **8** in 85% yield. The overall yield was 42.5%. The functionalised NCPS **9** (Fig. 1) was prepared[10] by copolymerising 4-vinylbenzyl chloride and styrene in a ratio of 1/3. The structure of the chiral auxiliary **8** was established by IR, NMR and elemental analysis. The spectra were consistent with the molecular structure.

We have previously reported[15] the preparation and application of a NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary, which was synthesised from N-Boc-*L*-tyrosine ethyl ester by a copolymerisation method in 28.8% overall yield.[15] We now report a new practical method for the synthesis of an NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary using the same starting material, and with an overall yield of 42.5%, which is higher than copolymerisation method.



Scheme 1 Synthesis of NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary.

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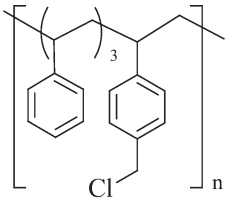

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Fig. 1 Functionalised NCPS.

Conclusion

This chiral auxiliary induced asymmetric alkylation reactions in good yield and stereoselectivity, and it was easily recovered and could be reused several times. The further application of the NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary to other asymmetric reactions, such as aldol reactions, Michael reactions and Diels–Alder reactions, is underway in our laboratory.

Experimental

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected; optical rotations were measured using the sodium D line on WZZ-2B Automatic Polarimeter; IR spectra were recorded on a PE IR-spectrum one spectrometer. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as the internal standard; elemental analyses were carried out with a VarioEL III (Germany) analyser. Gel permeation chromatographic analyses (GPC) were carried out on a μ-styragel preparative liquid chromatography (China) with a multi-angel laser photometer (DAWN HELEOS II, Wyatt, USA) and refractive index (RI) detector (Optilab Rex, Wyatt, USA) using a polystyrene standards.

O-Benzyl-L-tyrosinol (**4**): Obtained[16] from N-Boc-*L*-tyrosine ethyl ester **1** in 58.5% overall yield. The spectroscopic data of **4** correspond with those reported.[16]

N-2-(S)-(4-(4-Benzyloxy) benzyl) hydroxyethyl-N′-phenylthioureas (**5**): Phenyl isothiocyanate (2.0 mL, 16.34 mmol) in THF (10 mL) dropwise was added to a solution of compound **4** (3.5 g, 13.62 mmol) in THF (30 mL) and the mixture was stirred at 25 °C for 6 h. The solvent was removed under reduced pressure to afford a white solid. The crude product was further purified by column chromatography (EtOAc/PE, 1/5, v/v) to give **5** (5.30 g, 97%). m.p. 82.0–82.5 °C; $[\alpha]_D^{25} = -85.7$ (c 0.05, CH_2Cl_2); IR (NaCl): υ = 3367, 3250, 1732, 1610, 1596, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.44–6.88 (14H, m, ArH), 6.27 (2H, s, NH, OH), 5.04 (2H, s, OCH_2Ar), 4.78 (1H, s, -CH-N), 3.76 (1H, m, CH_2O), 3.61 (1H, t, *J* = 5.4 Hz, CH_2O), 2.85 (2H, m, CH_2Ar), 2.47 (1H, s, NHAr); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 180.1, 156.7, 136.9, 135.9, 130.2, 129.4 (6), 128.3 (2), 127.4 (2), 125.0 (2), 115.4 (2), 70.3, 60.5, 57.4, 35.7; Anal. Calcd for $C_{23}H_{24}N_2O_2S$: C, 70.38; H, 6.16; N, 7.14, S 8.17. Found: C, 70.26; H, 6.15; N, 7.08, S 8.33%.

(S)-4-(4-Benzyloxybenzyl)-2-phenylimino 2-oxazolidine (**6**): NaOH (0.99 g, 24.78 mmol) and *p*-toluenesulfonyl chloride (2.83 g, 14.87 mmol) in THF (20 mL) were added dropwise to a solution of compound **5** (4.86 g, 12.39 mmol) in THF (50 mL), then the mixture was stirred at 25 °C for 2 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (40 mL), and washed with brine (10 mL×3). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduce pressure to afford a yellow oil. The crude product was further purified by column chromatograph (EtOAc/PE, 1/8, v/v) to give **6** (4.12 g, 93%) as a colourless oil. $[\alpha]_D^{25} = -13.9$ (c 0.09, CH_2Cl_2); IR (NaCl): υ = 3312, 3032, 1644, 1595, 1551, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.45–7.14 (10H, m, ArH), 7.09 (2H, d, *J* = 7.8 Hz, ArH), 6.89 (2H, d, *J* = 7.8 Hz, ArH), 6.32 (1H, s, NH), 5.02 (2H, s, OCH_2Ar), 4.44 (1H, m, OCH_2), 4.23 (1H, m, OCH_2), 4.02 (1H, m, CH), 3.03 (1H, m, CH_2Ar), 2.78 (1H, m, CH_2Ar); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 157.8, 136.9, 135.8, 130.2 (2C), 128.7 (2C), 128.6 (2C), 128.0 (2C), 127.4 (3C), 123.5, 120.3, 115.3, 115.1 (2C), 72.5, 70.5, 68.9, 40.3; Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: 77.18; H, 6.22; N, 7.75%.

(S)-4-(4-Hydroxyl-benzyl)-2-phenylimino-2-oxazolidine (**7**): 20% $Pd(OH)_2$/C (0.43 g) and $HCOONH_4$ (1.15 g, 38.16 mmol) were added to a solution of compound **6** (3.26 g, 9.10 mmol) in EtOAc (20 mL) and CH_3OH (15 mL). The mixture was stirred at reflux for 3 h. After filtration of the catalyst and evaporation of the solvent, the crude product was further purified by column chromatography (CH_3OH/CH_2Cl_2, 1/30, v/v) to give **7** (2.31 g, 95%) as a colourless liquid. $[\alpha]_D^{25} = -87.5$ (c 0.008, CH_2Cl_2); IR (NaCl): υ = 3288, 1667, 1595, 1551, 737, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.25–7.17 (5H, m, ArH), 6.99 (2H, d, *J* = 7.8 Hz, ArH), 6.69 (2H, d, *J* = 8.4 Hz, ArH), 5.62 (2H, s, NH, OH), 4.42 (1H, m, CH), 4.15 (2H, d, *J* = 4.8 Hz, CH_2O), 2.75 (2H, d, *J* = 6.0 Hz, CH_2Ar); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.1, 155.7, 130.1, 128.9 (2C), 127.6 (2C), 123.1 (2C), 121.4 (2C), 115.8 (2C), 72.2, 61.3, 40.7; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.75; H, 5.92; N, 10.25%.

NCPS supported 2-phenylimino-2-oxazolidine (**8**): Functionalised NCPS **9** (5.12 g), anhydrous K_2CO_3 (16.26 g, 11.78 mmol), and 18-crown-6 (catalytic amount) were added to a solution of compound **7** (1.58 g, 5.89 mmol) in DMF (30 mL). The resulting mixture was stirred at 60 °C for 20 h. Then most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold ethanol (150 mL), and the precipitated solid was filtered and dried at 65 °C for 2 h under vacuum to afford polymer **8** (5.7 g, 85%). IR (NaCl): υ = 3321, 2925, 1680, 1598, 1509, 1241, 756, 699cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.30–7.18 (9H, m, ArH), 7.15–6.48 (bm, polymer-ArH); 6.15 (1H, s, NH), 4.23 (2H, m, CH_2O), 2.98 (2H, d, *J* = 8.4 Hz, CH_2Ar), 2.73 (1H, m, CH), 2.14–1.25 (bm, polymer-CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.3, 156.9, 148.5, 146.2, 134.2, 131.0, 129.4, 128.5, 126.8, 120.5, 114.4, 72.9, 70.3, 67.5, 40.2; Anal. Calcd for $C_{49}H_{48}N_2O_2$: C, 84.45; H, 6.94; N, 4.02. Found: C, 84.55; H, 6.92; N, 4.08%. The molecular formula was calculated by adding the sum of 1 mol 4-vinylbenzyl chloride and 3 mol styrene ($C_{33}H_{33}Cl$) to the molecular formula of **7** ($C_{16}H_{16}N_2O_2$) and then deducting HCl. The number average molecular weight (M_n) and molecular weight distribution (M_w/M_n) of polymer **8** were found to be 9000 and 1.4, respectively (gel permeation chromatographic analyses, calibrated by polystyrene standards).

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